Remarks

Responsive to the official action of April 22, 2002 please reconsider the outstanding rejections in view of the following remarks and information and allow all claims.

Claims 1-3, 7, 9-10 and 12-13 have been rejected under 35 U.S.C. 112 first paragraph for lack of enablement. The rejection is based upon the allegation that enablement is not provided for providing an oral secondary immune response to non-enteric pathogen antigens (NEPA's). This position by the Examiner is refuted, especially as it applies to the NEPA's selected from the group consisting of hepatitis C, hepatitis delta, yellow fever, dengue hemoragic fever, tetanus, staphylococcus aureous, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever as set forth in claim 3.

The rejection should be withdrawn since as previously discussed there is in fact clear enabling support in the specification, especially when considered in conjunction with the knowledge of one skilled in the art.

In making this rejection, the Examiner has said the specification "does not reasonably provide enablement for providing a secondary boosting response in a mammal to any and all NEPA's comprising the instantly claimed process steps and instantly claimed ingredients." and "the specification does not provide sufficient guidance as to how one of ordinary skill in the art would provide an immune response in a mammal and/or a human to a NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen."

The Examiner's statement is insufficient to support the rejection. Enablement is not solely dependent upon the precise words of the specification, but must also include the

knowledge of one skilled in the art. One skilled in the art clearly knows how to make the required genetically altered plant materials and in the 35 U.S.C. 103 rejections discussed infra, the Examiner has relied upon cited patents that clearly teach how to make the required plant materials and patents cited by the Examiner in fact have generically claimed such plant materials. This issue of enablement has thus already been decided by the U.S.P.T.O. For example, in the 35 U.S.C. 103 rejection, the Examiner has relied upon U.S. Patent 6,136,320 to Arntzen et al. Claim 1 of that patent says:

"An orally acceptable immunogenic composition comprising unpurified or partially purified recombinant viral immunogen expressed in a plant, wherein said immunogen is expressed in the plant at a level such that upon oral administration of said composition to an animal, an immunogenic response is observed."

Allowance of this claim clearly shows that the patent office has at least once accepted the fact that one skilled in the art now knows how to cause a plant to express a viral immunogen (antigen). If the Examiner were to maintain that one skilled in the art were not enabled to cause a plant to express an immunogenic viral antigen, he would, in essence, be taking a position that the patent he is relying upon contains an unsupported teaching and improperly supported claims. From a breadth perspective, the present application claims the same thing as U.S. Patent 6,136,320, except that in the presently claimed invention, it has been unexpectedly discovered that immunogens from non-enteric pathogens can be included that do not raise an oral primary immune response but can be used to obtain a secondary oral immunogenic response, if the animal is first vaccinated (non-orally). The teachings in the specification are more than adequate

to support this additional step for any viral immunogen within the previously accepted disclosure and claims of U.S. Patent 6,136,320.

The Examiner's attention is also drawn to U.S. Patent 5,679,880 in which claim 1 says:

"A transgenic plant, comprising and expressing a DNA sequence coding for an antigen of a pathogenic microorganism or an antigenic determinant thereof, said antigen or antigenic determinant thereof eliciting a secretory immune response in a human or other animal upon oral administration of tissue of said plant."

Similar disclosures and claims deemed supported by the U.S.P.T.O. are given in U.S. Patents 5,686,079 and 5,654,184.

Again it is clear that the U.S.P.T.O. has already decided that there is enablement for the base issues raised by the Examiner, i.e. one skilled in the art knows how to make plants and plant material expressing antigens from pathogenic microorganisms and further knows that they can be orally administered to obtain an immune response when the antigen is capable of eliciting such a response. The improvement in accordance with the present invention is that it has now been discovered that NEPA's which are otherwise not capable of eliciting any meaningful primary immune response orally, can be made to orally elicit a secondary immune response when the animal in question is previously vaccinated or immunized against the NEPA non-orally. This improvement is not obvious from the cited art but is clearly enabled by the teachings of the present specification in conjunction with the known state of the art.

The Examiner has further said "The art of virology, microbiology, and immunology are highly unpredictable because there are too many unknowns in the claimed process for the skilled

artisan to be enabled to practice the invention commensurate in scope to the claimed invention." With due respect to the Examiner, in this particular case, she is in error. Since the publication of the present invention after filing, persons skilled in the art have repeatedly practiced the invention with respect to other non-enteric pathogen antigens. The Examiner's attention is, for, example called to the article by Webster et al., "Successful Boosting of a DNA Measles Immunization with an Oral Plant-Derived Measles Virus Vaccine", Journal of Virology, August 2002, pp 7910-7912, where preparation of transgenic plants in the family *solanaceae* was illustrated and such transgenic plants were used to orally induce a boosting response against measles. The Examiner's attention is further called to Warzecha et al, "Oral Immunology of Human Papillomavirus Virus-like Particles Expressed in Potato", the published abstract of the Fifth Annual Conference on Vaccine Research, May 6-8, 2002 held in Baltimore, Maryland wherein the actual preparation of potatoes containing sequences from papilloma virus and their use for orally boosting immune reaction using sub-immunogenic doses. **The proof is in the reality. One skilled in the art is clearly enabled to practice the invention as claimed because persons skilled in the art are in fact doing so.**

Claims 1-3, 7, 9-10, and 12-13 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite.

This rejection should be withdrawn.

The objections to Claim 1, lines 2 and 3 have been obviated by prior amendment. The Examiner in arguing for ambiguity of the term "NEPA" is taking the definition of the term in the claims out of context leaving out the word "antigen" that is present in association with all

definitions of "NEPA". Claim 1 clearly says "...a specific antigen of a non-enteric pathogen (NEPA)...". Page 5, line 5 of the specification referred to and misquoted by the Examiner says "Non-enteric pathogen **antigen**" (NEPA) means an **antigen** that will parenterally raise an immune response to a non-enteric pathogen." (emphasis added). It is clear in the context of the claims and specification that "NEPA" refers to the antigen not to the entire pathogen. There is simply no ambiguity. Similarly, there is no ambiguity with respect to the fact that the active ingredient, i.e. NEPA, is in the vaccinating injection. Enumerating non-active ingredients is neither helpful nor required. Any person skilled in the art knows what vaccination by injection means. Further, it does not matter whether the vaccination is by a whole virus containing an NEPA or an isolated NEPA, so long as the NEPA is present and an immune response to the NEPA results. One skilled in art clearly knows this also.

The generic objection with respect to grammatical and idiomatic errors cannot be addressed. The generic objection is not understood. The objection is therefore improper and should be withdrawn.

The Examiner's objection to the lack of the word "boosting" in line 1 of amended claim 1 is formal in nature. The Examiner is correct that the omission of the word "boosting" is a typographical type error since the word "boosting" was never removed from claim 1 by the prior amendment. The word "boosting" is therefore still clearly present in line 1 of claim 1. A rewritten claim 1 correctly showing the amendments made in the last response is given below:

Claim 1 (as thrice amended by amendment mailed December 3, 2001)

A method for providing a secondary boosting immune response in a mammal to a specific antigen of a non-enteric pathogen (NEPA) , the pathogen being a pathogen that invades through a breach in the skin and that does not itself enterically raise a primary protective immune response in mammals in the absence of prior acquired immunity to the pathogen, said method comprising: rendering the mammal immunoreceptive to the NEPA by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection; and then orally administering the NEPA to the immunoreceptive mammal by feeding the mammal with transgenic potato containing the NEPA expressed in the potato to enterically cause a secondary immune response to the oral administration specific to the NEPA stronger than would be caused by orally administering the NEPA in the absence of the prior immunization by injection.

Claim 1 (as thrice amended by amendment mailed December 3, 2001 showing changes)

A method for providing a secondary boosting immune response in a mammal to a specific antigen [to] of a non-enteric pathogen (NEPA) , the pathogen being a pathogen that invades through a breach in the skin and that does not itself enterically raise a primary protective [enteric] immune response in mammals [free] in the absence of prior acquired immunity to the pathogen, said method comprising: rendering the mammal immunoreceptive to the NEPA by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection; and then [followed by oral] orally administering the NEPA to the [administration by feeding the]immunoreceptive mammal by feeding the mammal with transgenic potato containing the NEPA expressed in the potato to enterically cause a secondary immune response

to the oral administration specific to the NEPA stronger than would be caused by orally administering [a response specific to NEPA caused by] the NEPA in the absence of the prior immunization by injection.

It should, however be pointed out that the presence or absence of the word "boosting" in line 1 of claim 1 is irrelevant insofar as the meaning and breadth of the claim is concerned. The claim clearly requires providing a primary response followed by providing a secondary response. The provision of a secondary response as provided in claim 1 is known as a "boosting" response to one skilled in the art, whether or not the word "boosting" is actually present.

The Examiner has objected to claim 1 on the ground that "rendering the mammal immunoreceptive to the NEPA by injection" is indefinite on the ground that all mammals are immunoreceptive unless they have a compromised immune system. Again, the Examiner is taking terminology out of context. The exact "local" quote is "...rendering the mammal immunoreceptive to the NEPA by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection..." All normal mammals have limited immune response. As an example, normal mammals do not raise an immune response against "self" cells and do not rise an immune response against commonly encountered materials, e.g. water, vitamins, most carbohydrates, amino acids, etc. Normal mammals further do not raise an immune response to stimuli below a certain threshold concentration and may not raise a response to one method of exposure to an antigen while raising an immune response to another method of exposure to the same antigen. As an example some antigens may cause a serum response without causing a mucosal response and vice-versa. The present claims make it clear that the immune response in

question is specifically to an NEPA and not to any and all materials to which the mammal may or may not be immunoreceptive. The claims and specification further make it clear that the NEPA in question does not itself raise a protective enteric immune response in the absence of prior acquired immunity to render the mammal orally immunoreceptive to the NEPA. Normal mammals are not orally immunoreceptive to NEPA's unless they are first made orally immunoreceptive by prior immunization as claimed or by some other means. There is no ambiguity.

In view of the foregoing amendments and remarks, all objections and rejections under 35 U.S.C. 112 should be withdrawn.

Claims 1-3, 7, 9-10, and 12-13 have been rejected under 35 U.S.C. 103 as being unpatentable over Arntzen et al. (A, U.S. Patent 5,914,123) or Arntzen et al. (B, U.S. Patent 6,136,320 in view of Stites (U) and further in view of readily admitted prior art.

The rejection is improper and should be withdrawn for reasons previously discussed.

It is admitted that cited art discloses administration of immunogens expressed in plants to obtain an immune response; however, there is no suggestion of first administering the immunogen by injection and secondly administering the immunogen orally to obtain an oral response not otherwise obtained. None of the cited art in any combination suggests such a method. Such a concept is not obvious in view of the cited art. **Prior to the present invention, initial injection of an NEPA (alone or in a more complex viral package) followed by oral administration of the NEPA to obtain an immune response was never suggested and never tried.** Until the present invention, no person skilled in the art would have recognized that an

oral response to an NEPA, that does not normally yield an oral response, could be obtained by first obtaining a non-oral response, e.g. by injection.

The rejection is therefore clearly improper and should be withdrawn.

Arntzen et al. teaches a method for making a transgenic tobacco, tomato or potato that expresses HBsAg.

Notwithstanding the Examiner's assertion, **Arntzen et al. references do not teach "methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material."**

Arntzen et al. "A" itself teaches and recognize that not all antigens would cause an immune response if ingested **and there is no suggestion as to how to make NEPA's raise an oral immune response. Until the present invention, it was simply not obvious.**

Arntzen et al. "A" says in column 15 beginning at line 27,

"The vaccines are conventionally administered parentally, by injection, for example either subcutanously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, ***in some cases***, oral formulations or aerosols." (emphasis added).

But there is no teaching or suggestion in either Arntzen et al. reference of how the "some cases" could be determined or how the "some cases" could be accomplished.

While Arntzen et al. "A" suggests that tomato juice containing HBsAg **might** be used as a vaccine, in fact Arntzen provides no supporting data showing any immune response whatsoever to tomato juice or any other plant containing HBsAg. To the extent that the Arntzen et al. references teach that tomato juice or any other plant material containing HBsAg can be used as a

vaccine, they are inoperative references, since there is no teaching or suggestion as to how that might be done. ***Simply ingesting the plant material, as suggested by Arntzen et al., does not confer immunity.***

There is good reason for Arntzen's omission of data showing immune response to HBsAg by ingesting food material containing it, since prior to the present invention, in fact, there was little if any immune response whatsoever to HBsAg in orally ingested tomato juice or any other plant expressing HBsAg. **See the Rule 132 Declaration of Dr. Thanavala of record**. The response, if any, is clearly insufficient for that purpose.

Reference to the examples in the present specification clearly illustrates that priming of the subject of the immunization is required by either pre-vaccination or the use of an effective adjuvant. The Arntzen et al. references suggests neither. **The Arntzen et al. references simply do not suggest preimmunization by injection followed by oral feeding of a transgenic potato expressing a NEPA to obtain a secondary immune response as required by the present claims.**

Arntzen's suggestion of simple ingestion of plant material expressing HBsAg does not give a sufficient immune response to be considered protective. Arntzen discloses or suggests no way in which a high immune response could be orally obtained and the other cited references do not remedy that critical defect as previously discussed.

Simply making an unsupported suggestion in a reference without a teaching as to how the suggestion might be accomplished, is not a sufficient teaching to make a method for accomplishing the desired result obvious to one skilled in the art. Prophetic statements cannot

be used to form the basis of a rejection, especially when they are unsupported and not true. In using the word "may" Arntzen is not saying that a response will occur, but only that it "might". In fact, simple ingestion of tomato juice containing an NEPA does not raise a protective immune response as shown by the Thanavala declaration.

The Arntzen et al. B reference 6,136,320 pays lip service to raising an immune response by ingestion, but in fact give no examples or teachings for obtaining such a result. **The only actual plant examples in Arntzen et al. relate to tomatoes and tobacco. There is no example of ingestion of either one to raise a primary or secondary protective immune response.** In fact, ingestion of the transgenic tomato does not raise any significant immune response (see the Rule 132 Declaration of Dr. Yasmin Thanavala of record) and certainly whole tobacco cannot be used for such a purpose because it is toxic. **There is simply no teaching in either of the Arntzen et al. references of how oral immunization to any NEPA could be accomplished using a transgenic plant, and in fact the plants made in the Arntzen examples do not function orally to raise a primary protective immune response to any NEPA.** Arntzen certainly does not suggest that a potato expressing a NEPA could raise a secondary immune response when fed subsequent to immunization by injection, as presently claimed. **It is therefore clear that there is insufficient teaching or suggestion in the Arntzen et al. references to support a rejection of the present claims** whether or not the references are considered alone or in combination with Stites.

Stites et al. adds nothing to cure the inadequate teachings and suggestions of the Arntzen et al. references. Stites et al. does not suggest anything concerning orally raising an immune

response to an antigen expressed by a plant. Further, Stites et al. clearly does not suggest any method for **orally** raising a highly effective secondary immune response by feeding a potato expressing an antigen after prior injection of the antigen.

In view of the foregoing amendments and remarks, it is therefore courteously requested that all rejections be withdrawn and all claims be allowed.

Respectfully submitted,

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